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(71) Applicant
Yogo Takaoka,
8-291 Shibayama, Kanshuji, Yamaskina-ku, Kyoto, Japan

(72) Inventor
Yogo Takaoka

(74) Agent and/or Address for Service
Forrester, Ketley & Co.,
Forrester House, 52 Bounds Green Road, London N11 2EY

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A5B

(54) Treatment of athlete's foot

(57) A medicine for external application in the treatment of athlete's foot comprising at least 2,4,4'-trichloro-2'-hydroxy diphenylether as an anti-true fungi agent and urea as a horny substance softening agent, generally with hydrophilic ointment base, alcohol, or water, and optionally concentrated sulphuric acid.

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FIG.1

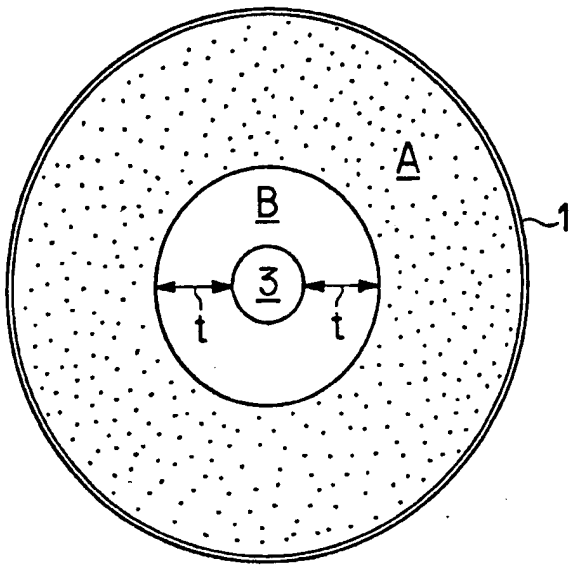


FIG.2

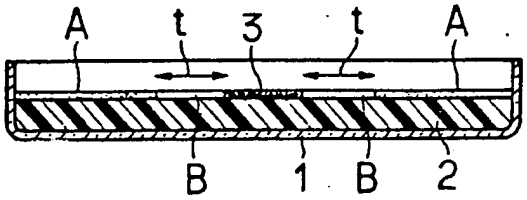
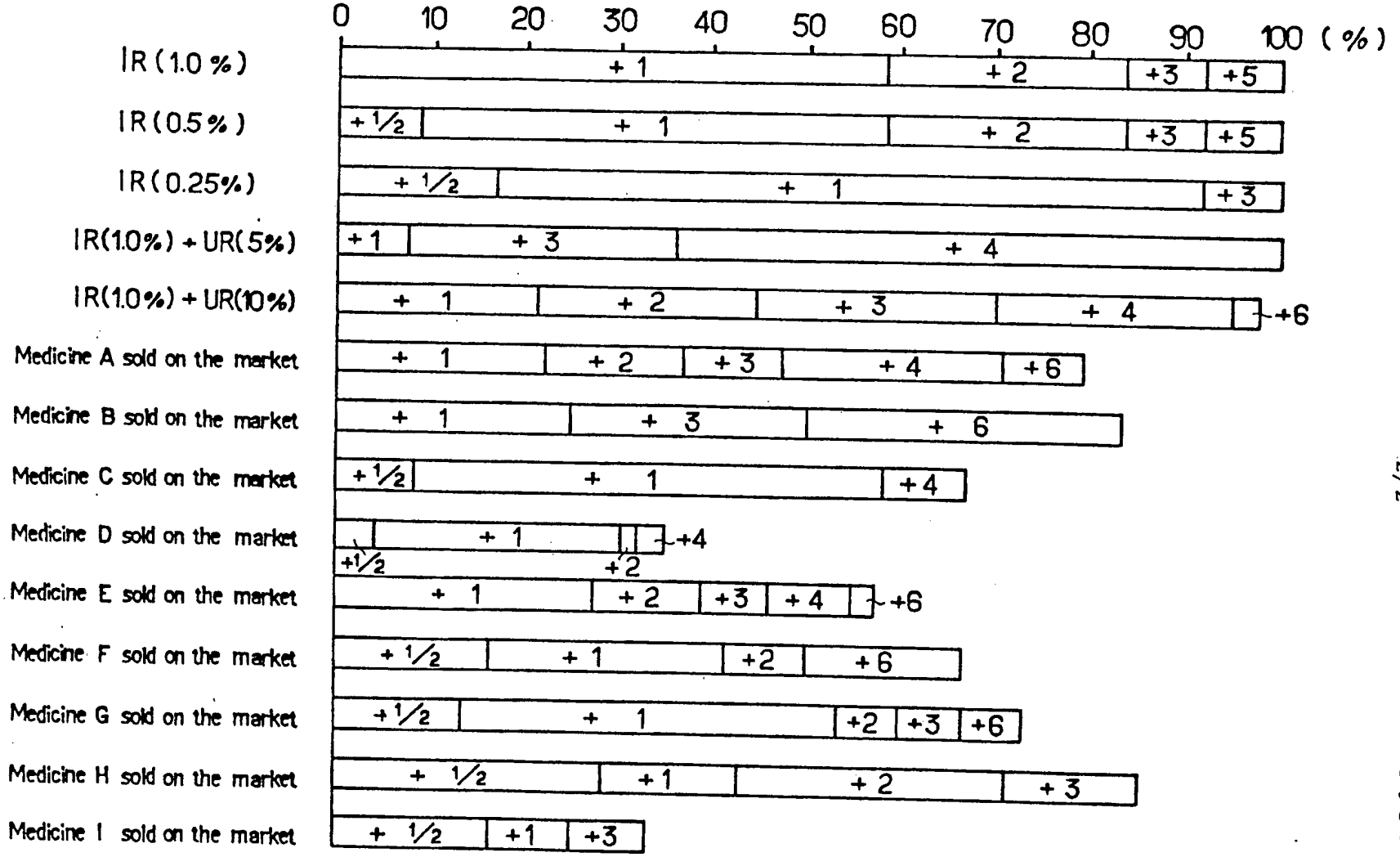


FIG. 3



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SPECIFICATION

Improvements in or relating to the treatment of athlete's foot

This invention relates to a medicine for use in the treatment of athlete's foot (tinea pedis or tinea pompholyciformis) which is a kind of skin disease, and more particularly to a medicine for external application in the treatment of athlete's foot to be used in the field of pharmacy.

An athlete's foot is a kind of skin disease caused by ringworm germ which can infest a part of a thick horny layer such as a sole of a foot or a palm.

Hitherto, many kinds of medicines have been proposed as medicines for external application in the treatment of athlete's foot and almost all of them performs a certain effect of preventing infestation of ringworm germ when tested in a test tube, and it can be said that there is not much difference in the aspect of effect among these conventional medicines. Athlete's foot is, however, a stubborn skin disease which does not yield completely to known medicines and, when apparently successfully treated, it is often the case that the germ still survives in the deep part of a horny layer of skin, to propagate again, so that the symptoms of athlete's foot return in the summer season or after suspension of the application of the medicine. This is because the ringworm germ is parasitic in the deep part of the horny layer into which the penetration of the medicine is difficult, and because the dermatophytosis germ is rather tough or resistant to medicine.

Accordingly, it is often the case that the experimental effect of a medicine does not always bring about the clinical remedial value expected and, therefore, athlete's foot is generally recognized as one of the stuborn skin diseases, which is difficult to completely cure. In order to cure this stubborn disease, it is usually recommended that the best way of treatment is to prove or determine exactly the kind of ringwork germ causing the infection, to select a most effective medicine for the identified germ, and patiently to apply the thus-selected medicine while keeping always the affected part (hand an foot) and the base parts between fingers or toes clean.In this way, the known medicine for athelete's foot is not always effective to cure the disease, depending on the kind of the ringworm germ, and it also occasionally happens that, although the medicine has been shown to be sufficiently effective in experimentation, the medicine is not in actual treatment. Thus, it is quite often that the disease makes a come-back in the affected part which had apparently been cured. In addition, it is necessary for the patient to have considerable patience with medical treatment over a long period.

Accordingly, it is an object of the present invention to provide a medicine for external application in the treatment of athlete's foot by which a successful clinical effect can be accomplished in a relatively short period irrespective of the kind of germ, that is, without determining the kind of ringworm germ before treatment is carried out, and the athlete's foot is completely cured, preventing the latter comeback thereof.

In accordance with this invention, there is provided a medicine for external application in the treatment of athlete's foot, which medicine contains at least 2,4,4'-trichloro-2'-hydroxy diphenylether and urea. The diphenylether and urea would generally be incorporated in a hydrophilic ointment base, alcohol, water or the like.

For a better understanding of the present invention, reference will now be made, by way of example, to the accompanying drawings, in which

Figure 1 shows a diagrammatic plan view for use in the explanation of a method of determining an anti-true fungi property of a medicine,

Figure 2 shows a longitudinal sectional view of Figure 1, and

Figure 3 shows a spectrum atlas for comparison of anti-true fungi property among various medicines.

An external application medicine for athlete's foot in accordance with this invention contains at least 2,4,4'-trichloro-2'hydroxy diphenylether as an anti-true fungi agent and urea as a softening agent.

Said 2,4,4'-trichloro-2'-hydroxy diphenylether is an anti-true fungi agent developed by Ciba-Geigy Limited (sold under the Trade name: Irgasan DP300), which is quite nonpoisonous in practical use, that is, it is an agent which does not cause any undesirable skin stimulation or reaction in the skin toxicity test being excellent in the adaptability to skin and widely used as fungicide or disinfectant (as in shown in "Medicine and Drug Journal" No. 2630, Japan Medical Journal pages 163-165, etc.). The preferable content of the 2,4,4'-trichloro-2'-hydroxy dipjenylether in said external application medicine for athlete's foot is from 0.2 to 2.0 weight % (or from 0.2 to 2.0 w/v %) and more particularly is approximately 1.0 weight % (or 1.0 w/v %).

The preferable content of the urea, which is a safe and low toxicity horny substance softening material, is from 5 to 40 weight % (or from 5 to 40 w/v %) and more particularly is approximately 10 weight % (or 10 w/v %).

Further, it is preferred to add a small quantity of sulfuric acid to said 2,4,4'-trichloro-2'-hydroxy diphenylether and urea, as a stabilizer. When the sulfuric acid is added thereto, both of the components (2,4,4'-trichloro-2'-hydroxy diphenylether and urea) are stabilized and as a result the effect of the medicine applied to the affected part continues long.

According to the external application medicine for athlete's foot of this invention, the water containing capacity of the skin is raised by the urea being one of the components so that the horny layer is softened by swelling. Accordingly, the medicine can easily penetrate into the deep part of the horny layer and at the same time the horny substance is gradually dissolved (liquefied) and separated (peeled), and as a result the horny layer itself becomes thin to promote the absorption of medicine through the skin, and finally the ringworm germ being parasitic on the horny layer is extinguished by the anti-true fungi component. Thus, even in case of varieties of germs or tough germs, they are completely extinguished by 2,4,4'-trichloro-2'-hydroxy diphenylether being excellent in anti-true germ effect.

Described hereinafter are experimental examples made for proving this invention. The scope of this invention, however, is not restricted to these experimental examples, as a matter of course.

[Example I]

In the first place, referring to Figure 1 and Figure 1, described is a method of obtaining an effectiveness (effect percentage) of a medicine to various true fungus (anti-true fungi spectrum) and an average effective germ propagation impeding index (anti-true fungi activity).

An agar is placed in a tray (1) to form a true fungi culture medium (2), and a true fungi is uniformly inoculatd into the culture medium (2). Then a specified quantity of medicine is absorbed in a filter paper (3) of 6 mm in diameter and, after being dried, the filter paper (3) is placed on the surface of the culture medium (2). By such arrangement, the medicine contained or absorbed in the filter paper is diffused throughout the agar, and if the medicine has an impeding property or effect against the germ propagation, 7-10 days after the culture or incubation, a ring band (B) where the true fungi is not propagated at all is formed between the filter paper (3) and a true fungi propagated area. In this example, the width (t) of said ring band (B) was measured, and an effective unit is decided based on Table 1 shown below:

TABLE 1

Width of ring band (mm)	0	0-1	1-3	3-5	5-7	7-9	9-11	over 11
Effective unit	0	+½	+1	+2	+3	+4	+5	+6

Then the effectiveness and the average effective germ propagation impeding index (hereinafter referred to as "average effective impeding index") of each medicine are calculated respectively by following formulas:

$$\text{Effectiveness (\%)} = \frac{\text{Number of test samples showing effective unit of } +\frac{1}{2} - +6}{\text{Total number of test samples}} \times 100\%$$

$$\text{Average effective impeding index} = \frac{\sum_{i=0}^{6}[(\text{effective unit: } +i) \times (\text{number of test samples})i]}{\text{Total number of test samples}}$$

The results of effectiveness (anti-true fungi spectrum) and average effective impeding index (anti-true fungi activity of various medicines are shown in Figure 3 and Table 2, where the respect to this invention the results, i.e., anti-true fungi effects of two examples prepared by dissolving 1.0g of 2,4,4'-trichloro-2'-hydroxy diphenylether and 5.0g and 10.0g of ureas into each 100 mℓ of 50% ethanol aqueous solution are shown (in Figure 3 and Table 2 they are shown as IR(1.0%) + UR(5%), IR(1.o%) + UR(10%) respectively). Further as a reference, the anti-true fungi effects of medicines prepared by dissolving 1.0 w)v %, 0.5 w/v % and 0.25 w/v % of 2,4,4'-trichloro-2'-hydroxy diphenylether into each 50% ethanol aqueous solution are shown (in Figure 3 and Table 2 they are shown as IR(1.0%), IR(0.5%) and IR(0.25%) respectively. In addition, the anti-true fungi effect of 9 kinds of external application medicines for athlete's foot obtainable in the market are also shown for the purpose of comparison.

TABLE 2

Medicine	*Number of samples*	*Effectiveness*	*Average effective impeding index*
IR(1.0%)	12	100	+1.75
IR(0.5%)	12	100	+1.63
IR(0.25%)	12	100	+1.08
IR(1.0%)+UR(5%)	14	100	+3.50
IR(1.0%)+UR(10%)	43	97.7	+2.60
Medicine A sold on the market	68	79.4	+2.29
Medicine B sold on the market	12	83.3	+3.00
Medicine C sold on the market	12	66.6	+0.88
Medicine D sold on the market	68	35.3	+0.43
Medicine E sold on the market	59	57.6	+1.25
Medicine F sold on the market	12	66.6	+1.50
Medicine G sold on the market	15	73.3	+1.20
Medicine H sold on the market	7	85.7	+1.29
Medicine I sold on the market	12	33.3	+0.42

As is explicit in Figure 3 and above Table 2, the medicine in accordance with this invention performs a very high effectiveness as compared with the external application medicines for athlete's foot sold on the market. In other words, the medicine composed of 2,4,4'-trichloro-2'-hydroxy diphenylether and urea has a wide range of anti-true fungi spectrum, which shows a superiority to the medicines sold on the market. Further, a high anti-true fungi activity was found being equivalent to the medicines A and B sold on the market (both of them are imidazole materials). In addition, as to the influence of the density of 2,4,4'-trichloro-2'-hydroxy diphenylether on the anti-true fungi effect, the result was that when the density was raised in the step of $0.25<0.5<1.0$ w/v %, the anti-true fungi effect became higher as accordingly. When the density is more than 2.0 w/v %, however, the anti-true fungi effect by the increase of density did not change any more, although not shown in the drawing and table. Also it was found that the anti-true fungi effect was higher when the 2,4,4'-trichloro-2'-hydroxy diphenylether was used together with urea than when it was used alone.

With respect to the density of urea, any particular significance was recognized in the aspect of horny substance dissolving and separating effect between 10 w/v % and 20 w/v %, but in comparison between 5 w/v % and 10 w/v %, the latter showed an excellency from the clinical point of view.

[Example II]

Then, described is an example of a stabilizer for stabilizing both 2,4,4'-trichloro--2'-hydroxy diphenylether and urea contained in the medicine. An experiment was effected by preparing 4 kinds of solutions shown in Table 3 (wherein "2% IR ethanol solution" means a 2 w/v % ethanol (99.5%) solution of 2,4,4'-trichloro-2'-hydroxy diphenylether).

TABLE 3

	20% urea aqueous solution	*2% IR ethanol solution*	*Glacial acetic acid*	*Concentrated sulfuric acid*	*50% ethanol aqueous solution*	*1N caustic soda*	*50% ethanol aqueous solution*
a	1 mℓ	1 mℓ	0.05 mℓ	–	–	–	0.5 mℓ
b	1 mℓ	1 mℓ	–	0.05 mℓ	–	–	0.5 mℓ
c	1 mℓ	1 mℓ	–	–	0.05 mℓ	–	0.5 mℓ
d	1 mℓ	1 mℓ	–	–	–	0.5 mℓ	0.05 mℓ

The stability of the medicine was evaluated by obtaining each decomposition quantity of the urea and the 2,4,4'-trichloro-2'-hydroxy diphenylether after leaving 2.55 mℓ of each prepared solution for 72 hours at 37°C.

With respect to the stability of urea, when it is decomposed, an ammonia is produced, and accordingly the stability thereof was tested by measuring the produced quantity of ammonia.

$$CO(NH_2)_2 + H_2O - 2NH_3 + CO_2$$
(urea) (water) (ammonia) (carbon dioxide)

where, 1 mℓ of prepared solution contains 0.07843g of urea, and when this urea is decomposed, 0.04448g of ammonia is to be produced. Accordingly, the ammonia production percentage was calculated by the formula,

$$\frac{\text{measured ammonia quantity (g)}}{0.04448\text{g}} \times 100\ (\%).$$

In this connection, as a measuring method of ammonia, a so-called Fujii-Okuda method is employed. The result is as per Table 4.

TABLE 4

Prepared solution	*Ammonia production %*	*IR decomposition %*
a	0.068	38.6
b	0.051	2.9
c	0.052	22.9
d	0.051	24.8

As is obvious from the above table, the stability of urea is more excellent or sufficient when concentrated sulfuric acid is added to the prepared solution than when acetic acid is added thereto. When using other additive agent than said concentrated sulfuric acid and acetic acid such as pyruvic acid produced by oxidation-reduction reaction of lactic acid, since the decomposition of urea advances as the density increase of the pyruvic acid, it is not suitable as a stabilizer. Further, when using hydrochloric acid, a crystal precipitation is easily caused by the production of salt, and when using citric acid, EDTA·2Na or EDTA·2K, any of them reacts on calcium ion of the skin surface to produce chelate compound. Thus, said agents are not suitable to be used as stabilizer.

Described now is a stabilizer for the 2,4,4'-trichloro-2'-hydroxy diphenylether. In this connection, since a phenolic compound makes a condensating reaction on 4-aminoantipyrin to produce a quinone type pigment, a quantitative analysis of 2,4,4'-trichloro-2'-hydroxy diphenylether was effected by measuring the absorptivity thereof at 500 nm (or (570 nm). And the decomposition percentage was calculated based on the quantitative difference between the quantity before leaving it 72 hours at 37°C and the quantity after such leaving. The result is as per Table 4 (in this table the "IR decomposition %" means a decomposition percentage of 2,4,4'-trichloro-2'-hydroxy diphenylether).

As is seen from Table 4, the stability is quite sufficient when adding the sulfuric acid a little to the prepared solution. Since the addition of a small quantity of sulfuric acid is not only useful for stabilizing the urea as aforementioned but also effective for stabilizing the 2,4,4'-trichloro-2'-hydroxy diphenylether, it is concluded that the small quantity of sulfuric acid is a best stabilizer for stabilizing both of said two materials.

[Example of Application]

Referring now to one example of actual application of the external application medicine for athlete's foot in accordance with this invention, 1.0g of 2,4,4'-trichloro-2'-hydroxy diphenylether and 10.g of urea are mixed or kneaded with 89.0g of hydrophilic ointment base, and the medicine thus composed is applied to an affected part once a day after being cleaned the affected part by rubbing off the swallen outer layer of the skin with towel or the like after taking a bath. Then, the athlete's foot is cured after repeating said treatment for 4-5 days in case of a slight disease or 2-3 weeks in case of serious disease.

It is also preferred that, as a modification, either the ointment prepared by the above-described manner or the solution prepared by dissolving the 2,4,4'-trichloro-2'-hydroxy diphenylether into an ethanol aqueous solution or the like is applied together with some adhesive material to one side of a tape to form an adhesive tape, covering the affected part thereby. In case of employing this application method, as compared with the ordinary external application of the ointment to the affected part, even when the density of the medicine is 1/10-1/20 of the ointment, a quite satisfactory medical effect is achieved.

The medicine for athlete's foot in accordance with this invention is not limited to the application to the skin but applicable to the ringworm of rail. In this case, it is preferred to prepare the medicine by admixing 1g of 2,4,4'-trichloro-2'-hydroxy diphenylether, 40.0g of urea, 24.0g of refined lanolin, 25.0g of white vaseline and 10.0g of bleached beeswax and to apply it to the affected nail.

CLAIMS

1. A medicine for external application in the treatment of athlete's foot, which medicine contains at least 2,4,4'-trichloro-2'-hydroxy diphenylether and urea.
2. A medicine according to Claim 1, which also contains a small quantity of concentrated sulfuric acid.
3. A medicine according to Claim 1 or 2, wherein from 0.2 to 2.0 weight % of 2,4,4'-trichloro-2'-hydroxy diphenylether and from 5 to 40 weight % of urea are admixed in a hydrophilic ointment base.
4. A medicine according to Claim 1, 2 or 3, which contains 1.0 weight % of 2,4,4'-trichloro-2'-hydroxy diphenylether and 10 weight % of urea.
5. A medicine according to Claim 1 or 2, wherein from 0.2 to 2.0 w/v % of 2,4,4'-trichloro-2'-hydroxy diphenylether and from 5 to 40 w/v % of urea are dissolved in 50 % aqueous ethanol.
6. A medicine according to Claim 5, which contains 1.0 w/v % of 2,4,4'-trichloro-2'-hydroxy diphenylether and 10 w/v % of urea.
7. A medicine for external application in the treatment of athlete's foot and in accordance with Claim 1, substantially as described in any foregoing Example.
8. Any novel feature or combination of features described herein.

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